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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,423	08/25/2003	Sergei G. Bavykin	21416-94731	5272

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EXAMINER	
WOOLWINE, SAMUEL C	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/647,423	BAVYKIN ET AL.	
	Examiner	Art Unit	
	Samuel Woolwine	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-12,16,17 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-12, 16, 17 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status

Claims 10-12, 16, 17 and 20 are pending. Claims 11, 17 and 20 have been amended since the previous Office action of 3/21/2006 in which claims 10-12, 16, 17 and 20 were rejected. Any rejection not reiterated below has been withdrawn as no longer applicable.

Claim Rejections - 35 USC § 112 –Response to arguments

The rejection of claims 11 and 17 in the previous Office action are withdrawn in view of Applicants' amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10-12, 16, 17 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitsuhashi (US Pat 5,580,971) in view of Ash et al (1991), Chee et al (1996), Ash et al (1992) and Genbank Accession Nos (GI Nos) 3929652, 8452887, 3929664, 3929662, 927390, and 1149455.

With regard to claims 10 and 20, Mitsuhashi teaches a method comprising placing on a microchip oligonucleotide probes targeted to rRNA sequences (see figure 2), providing conditions for hybridization of the probes with rRNA from the sample (see column 1 line 50 through column 2 line 20), and analyzing hybridization signals in the

microchip from which the particular isolate is detected (see column 2 lines 35-45). In this case, the "microchip" (which is not explicitly defined or otherwise limited by Applicant's disclosure) is a microtiter plate (see column 1 lines 50-60). Mitsuhashi does not teach probes corresponding to the specific oligonucleotide probes of claim 10.

Ash teaches a method for the discrimination among *B. anthracis, B. cereus, B. mycoides,* and *B. thuringiensis* based on 16s rRNA sequencing, wherein at least one mismatch is sufficient to discriminate among these members (see Table 2). In fact, at least two of the mismatches (see Table 2, position 92/94 and position 1,005 and see Figure 1) correspond to the mismatches used by Applicant in the SEQ ID NO 86/87 and 74/75 probe pairs. Ash does not teach the specific oligonucleotide probes of claim 10, or the use of a microchip, hybridization, or analysis of hybridization signals for distinguishing among the members of the *B. cereus* group.

Chee teaches the use of oligonucleotide microchip arrays for the discrimination of sequences having a single nucleotide mismatch (see page 611, column 1, 1st sentence of 1st full paragraph, and see Figure 1). Chee does not teach the use of such an array for the discrimination among members of the *B. cereus* group, but does teach that "[t]he methods described are generic and can be used to address a variety of questions in molecular genetics including gene expression, genetic linkage, and genetic variability" (see abstract). Chee does not teach the use of the specific oligonucleotide probes of claim 10.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to combine the discriminating

polymorphisms taught by Ash with the oligonucleotide arrays taught by Chee to arrive at the microarray of claim 10 in order to discriminate among species based on rRNA hybridization as taught by Mitsuhashi. Motivation to do so is clear since the polymorphisms taught by Ash are single nucleotide mismatches, and Chee teaches that the array is able to detect polymorphisms "with single-base resolution" (see abstract). Chee also teaches that hybridization-based methods using oligonucleotide microchips have higher throughput capacity than conventional sequencing based methods such as those used by Ash et al (see Chee page 612, column 3, 2nd full paragraph).

Ash teaches that "[s]mall-subunit rRNA is now recognized as a powerful molecular chronometer" and Applicant agrees (on page 2 of the specification of provisional application 60/336,319 upon which priority of the instant application is based) that "[h]ybridization analysis of the 16S rRNA is a well established method of microbial identification" (references omitted). Since Ash also teaches that "[o]nly 11 base substitution points on the sequences were identified" (comparing the 16s rRNA sequences of *B. anthracis, B. cereus, B. mycoides,* and *B. thuringiensis*, see page 345, column 1), one of ordinary skill would clearly have been motivated to use these polymorphisms when designing discriminating oligonucleotide probes.

Chee teaches the use of discriminating single nucleotide polymorphisms using a matched set of probes in which the variant nucleotide resides in the middle of the probe (see figure 1, panels A and B). This is based on the sound scientific reasoning that placing the mismatch in the middle of the probe would minimize the length of continuous complementarity, thus resulting in the lowest melting temperature between probe and

mismatched target, thus maximizing the difference in melting temperature between perfectly matched and mismatched sequences. Therefore, one of ordinary skill in the art would be motivated to design a oligonucleotide probe microarray in which the variant nucleotides identified by Ash would reside in the middle, resulting in the claimed microarray comprising probes corresponding to the SEQ ID NO 86/87 and 74/75 probe pairs. Note that while one of ordinary skill might have ended up with probes with minor differences from the SEQ ID NO 86/87 and 74/75 probe pairs (i.e. with one or more additional or fewer nucleotides at either end), such minor differences would not be considered unobvious in view of *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), in which the Court of Appeals for the Federal Circuit stated regarding structural or functional homologs:

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties"

Since the claimed probes simply represent functional homologues of probes that would have been obvious to one of skill in the art at the time, the claimed microarray is *prima facie* obvious in the absence of secondary considerations.

With regard to claims 11 and 12, the arrangement of oligonucleotide probes on the array is simply a matter of design choice (see MPEP 2144.04, VI, C Rearrangement of parts). In the absence of secondary considerations, the arrangement of oligonucleotide probes on the array would not affect the performance of the microarray in terms of its ability to discriminate among the various *Bacillus* strains.

With regard to claims 16 and 17, since the microarray of claims 10-12 and 20 are *prima facie* obvious as discussed above, the probes on the array are also *prima facie* obvious, since one could not construct the microarray without also synthesizing the probes.

With regard to all claims, it is further noted that all of the sequences of SEQ ID NOS 88-91 and 126-127 were known in the prior art to be contained within either the 16s or 23s rRNA sequences from *Bacillus* strains as evidenced by Genbank Accession Nos (GI Nos) 3929652, 8452887, 3929664, 3929662, 927390, and 1149455. The teachings of Ash (1991, 1992) as to the relative rarity of polymorphisms in these sequences among members of the *B. cereus* group would provide clear motivation to one of ordinary skill to choose the polymorphisms represented by said SEQ ID NOS to distinguish members of the *B. cereus* group as discussed above.

SEQ ID NO 88 (reverse complement):

```
>┌ gi|3929652|emb|Y18473.1|BTH18473  Bacillus thuringiensis 16S rRNA gene, strain WS2623
         Length=1474

 Score = 40.1 bits (20),  Expect = 4e-04
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Plus

Query  1     GCTTCTCCTTCGGGAGCAGA  20
             ||||||||||||||||||||
Sbjct  983   GCTTCTCCTTCGGGAGCAGA  1002
```

SEQ ID NO 89 (reverse complement):

```
>gi|8452887|gb|AF155957.1|AF155957  Bacillus mycoides strain 10206 16S ribosomal RNA gene, partial
          sequence
         Length=1508

 Score = 40.1 bits (20),  Expect = 6e-04
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Plus

Query  1     GCTTCCCCTTCGGGGGCAGA  20
             ||||||||||||||||||||
Sbjct  1021  GCTTCCCCTTCGGGGGCAGA  1040
```

SEQ ID NO 126:

```
>gi|3929664|emb|Z84594.1|BTH84594  Bacillus thuringiensis 16S rRNA gene, strain WS 2617
         Length=2175

 Score = 40.1 bits (20),  Expect = 4e-04
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Minus

Query  1     TTTGGGCTATGTTCCGTTTC  20
             ||||||||||||||||||||
Sbjct  1924  TTTGGGCTATGTTCCGTTTC  1905
```

SEQ ID NO 127:

```
>gi|3929662|emb|Z84592.1|BCE84592  Bacillus mycoides 16S rRNA gene, strain DSM 2048T
         Length=832

 Score = 40.1 bits (20),  Expect = 0.027
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Minus

Query  1     TTTGGGCTAGATTCCGTTTC  20
             ||||||||||||||||||||
Sbjct  580   TTTGGGCTAGATTCCGTTTC  561
```

SEQ ID NO 90:

```
>gi|927390|emb|X89895.1|BT16S23S  B.thuringiensis DNA for 16S and 23S rRNA and spacer region
         Length=2978

 Score = 40.1 bits (20),  Expect = 0.027
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Minus

Query  1     CAGCTCAGCCTTCACGATAA  20
             ||||||||||||||||||||
Sbjct  1768  CAGCTCAGCCTTCACGATAA  1749
```

SEQ ID NO 91:

```
>┌ gi|1149455|emb|X94448.1|BC16S23SD  B.cereus 23S rDNA and 16S-23S spacer region
        Length=2978

 Score = 40.1 bits (20),  Expect = 0.027
 Identities = 20/20 (100%), Gaps = 0/20 (0%)
 Strand=Plus/Minus

Query  1     CAGCTCAGCCTTTACGATAA  20
             ||||||||||||||||||||
Sbjct  1767  CAGCTCAGCCTTTACGATAA  1748
```

Claim Rejections - 35 USC § 103 –Response to arguments

Applicant's arguments filed 6/21/2006 have been fully considered but they are not persuasive.

Some of Applicant's arguments are simply that one of the references upon which the rejection is based fails to teach a claimed limitation, or teaches something different than is accomplished by the claimed invention. For example, on page 6 of the response, Applicant states: "Misuhashi relates to fungi, not bacteria...". On page 7, Applicant states: "Chee relates analysis of human mitochondrial DNA, not *Bacillus* and not rRNA...". Such arguments are not persuasive because the rejection is based on the combination of references. In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant also argues that the references teach methods, not compositions. For example, on page 6 of the response Applicant states: "The examiner cites Mitsuhashi for a **method**, but neither claim 10 nor 20 relates a method, so the Mitsuhashi

publication as the examiner uses it – is not relevant to claims 10 and 20." This argument is not persuasive because the combination of references used in the rejection sets forth each limitation of the claims as described in the rejection. Whether a combination of references teaches a composition *per se*, or whether is teaches a method in which a composition is used, makes no difference. So long as all limitations of the claims are taught or suggested, a rejection is proper.

Applicant argues that Ash does not teach "distinguishing Anthracis" (bottom of page 6 of the response). Ash (1991) clearly distinguishes B. anthracis from other Bacillus species based on differences in rRNA sequences (for example, in Table 2).

Applicant argues on page 7 that "[t]he examiner sloughs off probe design as justification for those claimed as obvious because of Ash giving an opinion that 'small subunits in RNA' are useful, and because full sequences of Bacillus are known". This argument seems to imply that just because Ash expresses the opinion that "[s]mall-subunit rRNA is now recognized as a powerful molecular chronometer", such opinion does not render the claimed probes obvious. This argument is not persuasive because the rejection is not based on Ash alone, but on the combination of references serving as the basis for the rejection. Furthermore, Applicant states (on page 2 of the specification of provisional application 60/336,319 upon which priority of the instant application is based) that "[h]ybridization analysis of the 16S rRNA is a well established method of microbial identification", which actually supports Ash's justification to determine "16S rRNA sequences of B. anthracis, B. cereus, B. mycoides and B. thuringiensis in order to

investigate the genealogical interrelationships among these organisms" (Ash, 1991, page 343, column 1, last sentence of second paragraph).

Applicant further argues on page 7 that there is no guidance cited by the examiner that would lead to the claimed probes, and that the design and composition of the claimed probes is not obvious. In fact, the obviousness of the claimed probes is clearly spelled out in the rejection. To summarize:

- Applicant states (on page 2 of the specification of provisional application 60/336,319 upon which priority of the instant application is based) that "[h]ybridization analysis of the 16S rRNA is a well established method of microbial identification" (references omitted). This constitutes admitted prior art.
- Ash (1991 and 1992) teaches that among different isolates of the genus *Bacillus*, only a few sequence differences (single nucleotide polymorphisms) are found in the 16s and 23s rRNA sequences (see Ash 1991, page 345, column 1 and Ash 1992, figure 2).
- Mitsuhashi teaches immobilized oligonucleotide probes to rRNA sequences can be used to identify microorganisms (see figure 2).
- Chee teaches that oligonucleotide microarrays can discern single nucleotide differences between sequences (see page 611, column 1, 1st sentence of 1st full paragraph, and see Figure 1).
- All of the *Bacillus* rRNA polymorphisms found in the claimed probes were known in the art (see alignments above).

- Buck provides evidence for the equivalence of primers/probes to a target sequence with regard to the ability to hybridize to a target [and be extended] (see discussion of Buck above).

Applicant argues on page 8 that the set of 10 probes is not contained in the compilation of publications and nucleotides cited. This is not persuasive because as shown by the alignments of the rejection, all of the Bacillus rRNA sequence differences encompassed by the claimed probes were known in the prior art.

Applicant points out specific features or capabilities of the claimed probes and arrays on pages 8 and 9 of the response. Such features or capabilities are not in dispute. This issue is whether such probes and arrays would have been obvious to one of ordinary skill in the art at the time the invention was made. Based on the discussion presented in the rejection, it is clear that such probes and arrays would have been considered obvious to the ordinary practitioner.

Applicant argues on page 9 that, in regard to claims 11 and 12, the particular positions of the probes on the array represents a novel, presumably patentable feature. This is not persuasive because the pattern in which the probes are placed on the claimed array would not be expected to function any differently or produce any better or worse results than any other pattern in which the same probes were placed on the array.

Finally, Applicant argues on pages 9 and 10 that "the examiner applies his own reasoning, based on hindsight, to construct a story that the claimed probes would have been designed by those of skill in the art". In response to applicant's argument that the

examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The combination of references cited by the examiner teach or suggest each limitation found in the claims. The motivation to combine or modify the teachings of individual references is clearly stated throughout the rejection. Therefore the rejection of claims are proper.

Double Patenting

Claims 10, 11, 12, 16, 17 and 20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9, 10, and 12 of copending Application No. 10/287,455. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 9 and 10 of the '455 case are drawn to a microarray comprising sequences identical to SEQ ID NOS: 74, 75, 86, 87, 88, 89, 90, 91, 126, 127. Claim 12 of the '455 case is drawn to probes with identical sequence to SEQ ID NOS: 74, 75, 86, 87, 88, 89, 90, 91, 126, 127.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Double Patenting –Response to arguments

The provisional double patenting rejection of the previous Office action is maintained because a terminal disclaimer has not been filed, and no arguments were presented for consideration by the examiner.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Woolwine whose telephone number is (571) 272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SCW

JEFFREY FREDMAN
PRIMARY EXAMINER
8/11/06